

P = POLAR GROUP
N = NONPOLAR GROUP

FIG. 1

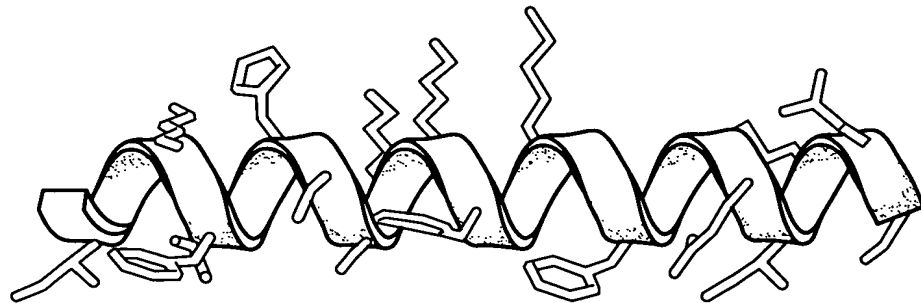


FIG.2

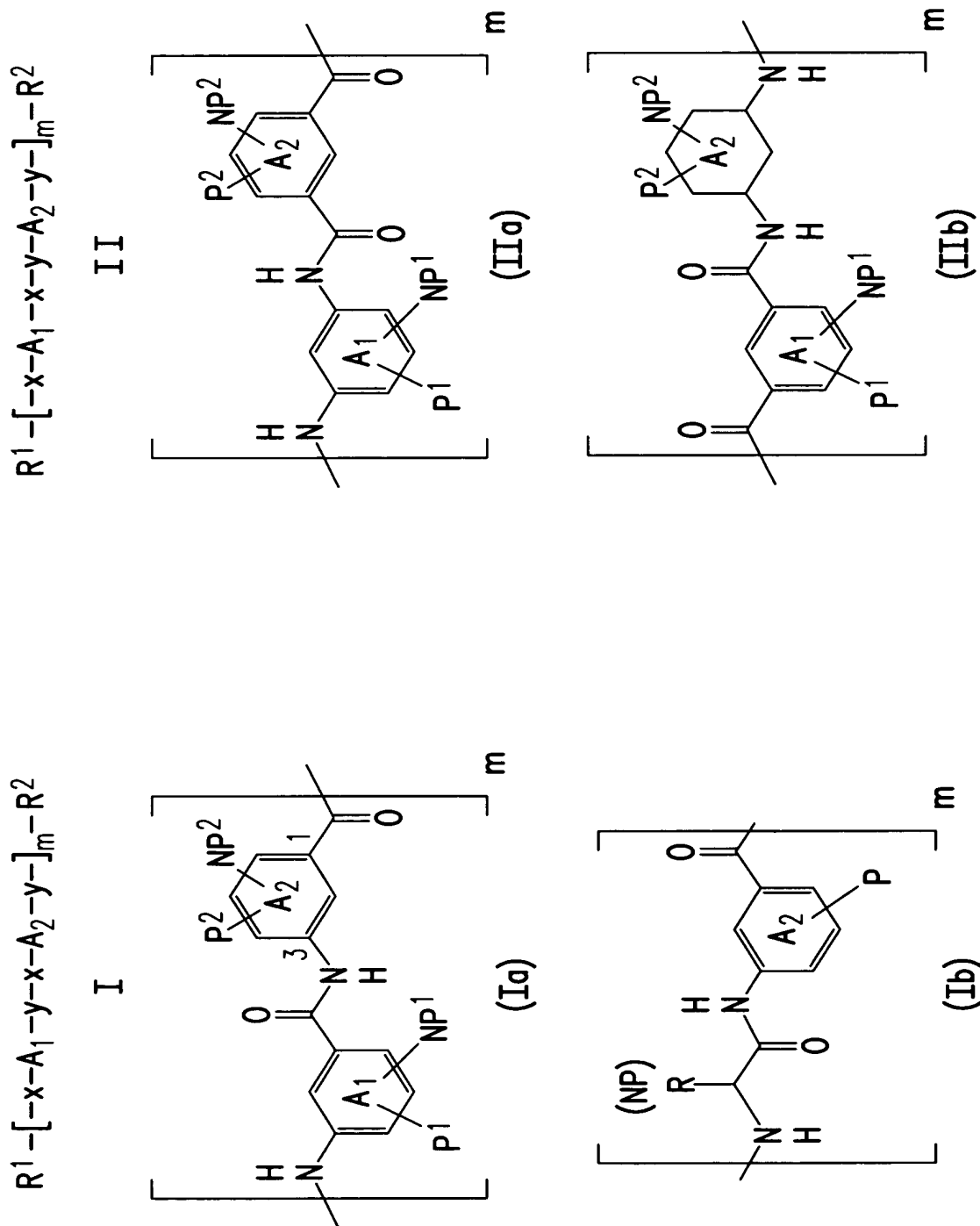


FIG.3

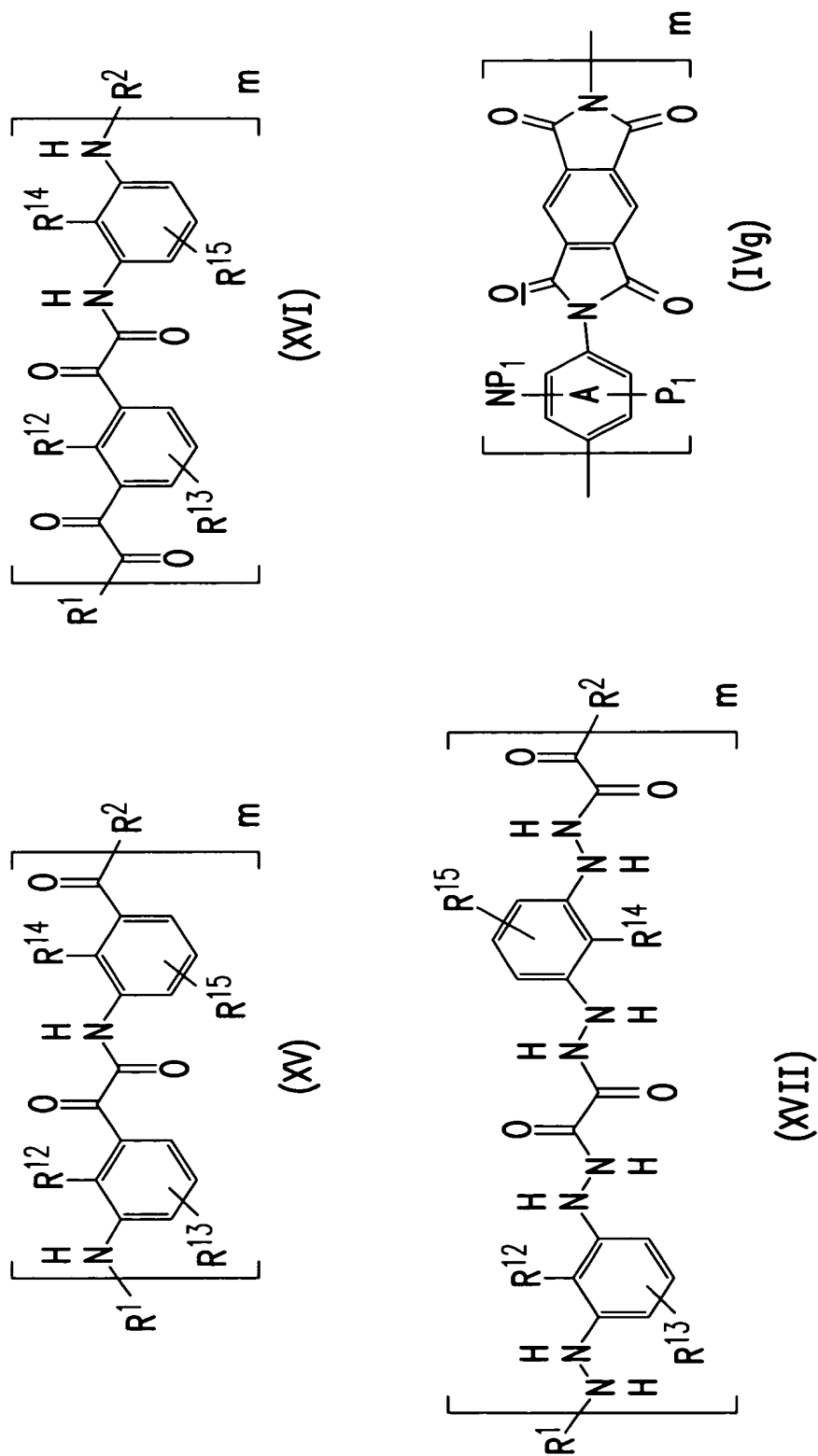
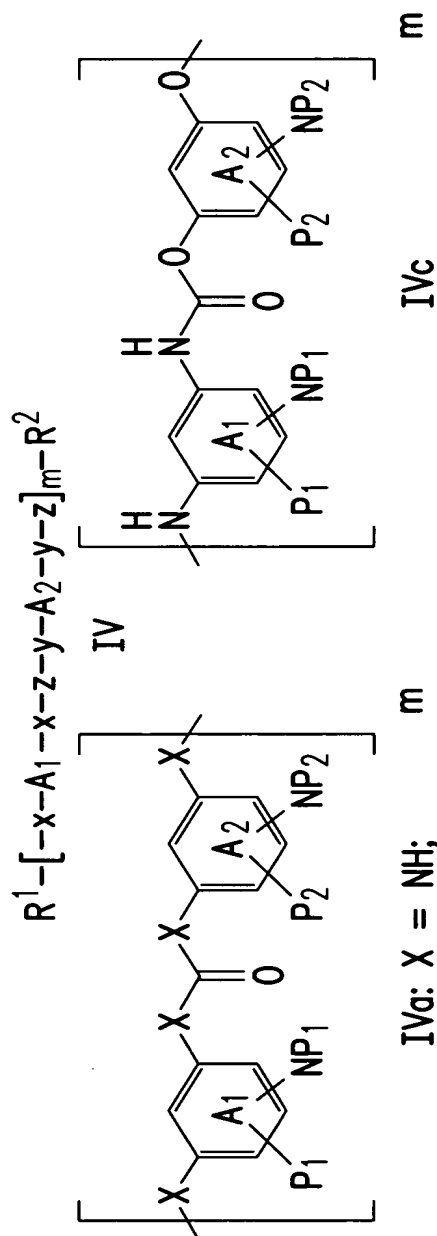
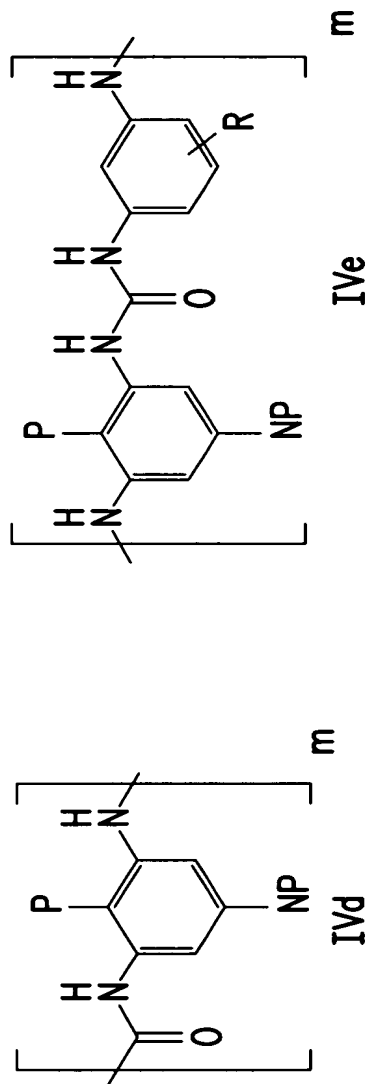


FIG.4



IVa: X = NH;
 IVb: X = O.



P	NP1	R
O-CH2-CH2-NMe2	O-CH2CH3	O-CH2-CH2CH3
O-CH2-CH2-(2-PYRIDYL)	O-CH2CHMe2	O-CH2CH2CH(CH3)2
O-CH2-CH2N(CH2-CH2-NMe2)2	O-CHMe2	O-CH2CH2CH2CH3
O-CH2-CH2-(2-IMIDAZOLYL)	OCMe3	O-CH2-CH3
O-CH2-CH2NH-C(=NH)NH2	O-CH2-CHMe2	O-CH2-CH2CH3
O-CH2-CH2N(CH2CH2)2NH	O(CH2)4Me	O-CH2CH2CH2CH3

FIG. 5

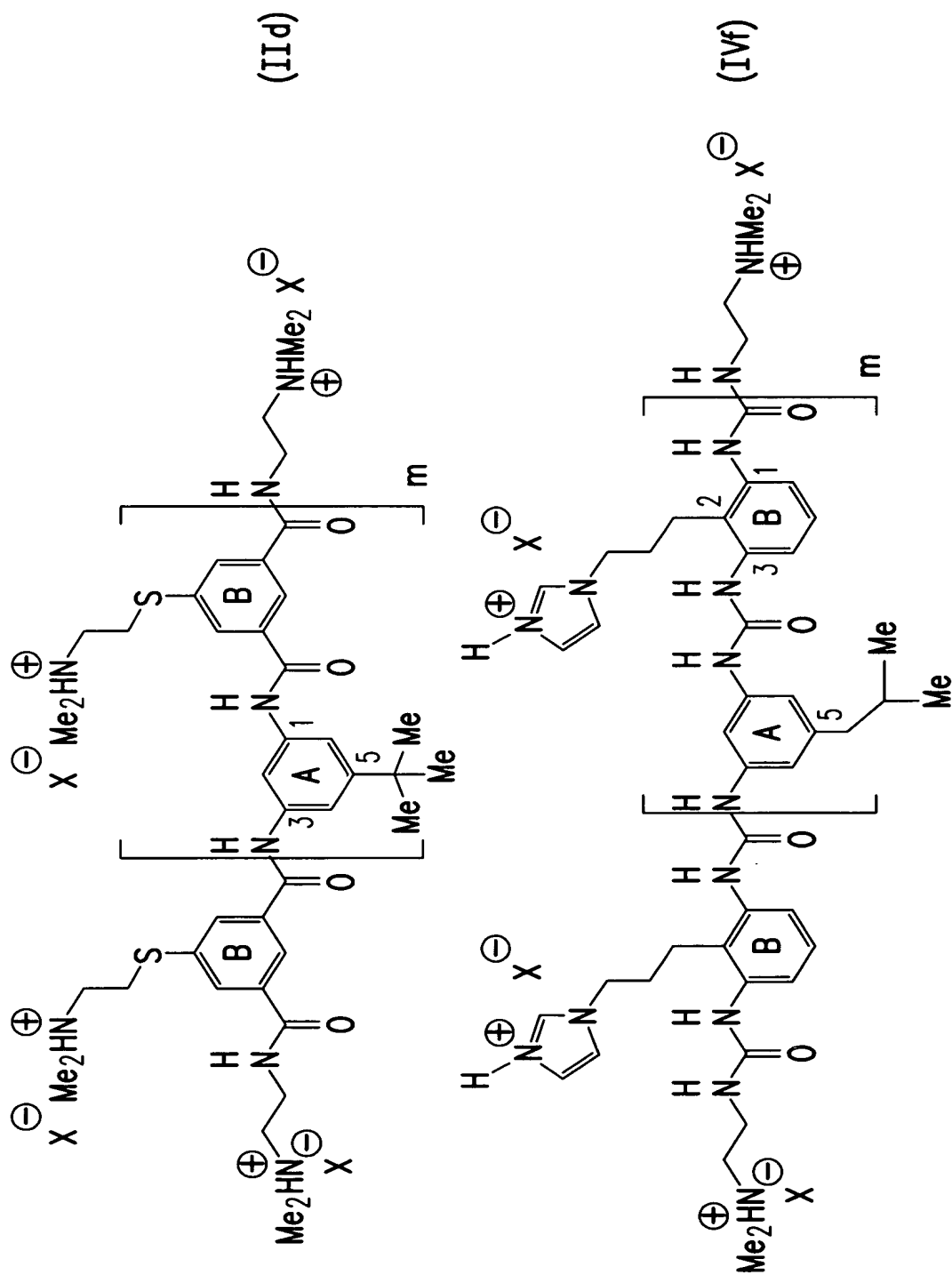
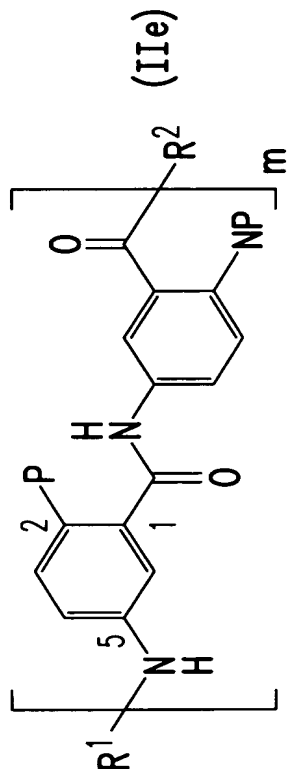


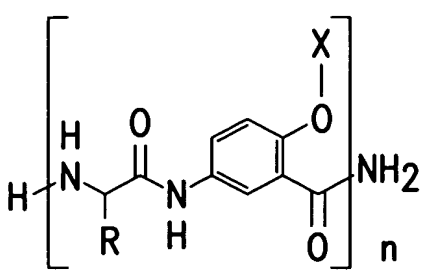
FIG.6



P	NP1
O-CH ₂ -CH ₂ NMe ₂	O-CH ₂ CH ₃
O-CH ₂ -CH ₂ -(2-PYRIDYL)	O-CH ₂ CHMe ₂
O-CH ₂ -CH ₂ N(CH ₂ -CH ₂ -NMe ₂) ₂	O-CHMe ₂
O-CH ₂ -CH ₂ -(2-IMIDAZOLYL)	OCMe ₃
O-CH ₂ -CH ₂ NH-C(=NH)NH ₂	O-CH ₂ -CHMe ₂
O-CH ₂ -CH ₂ N(CH ₂ CH ₂) ₂ NH	O(CH ₂) ₄ Me

FIG. 7

F/G.8

			ANTIMICROBIAL ACTIVITY MIC ($\mu\text{g/mL}$) ¹			HEMOLYTIC ACTIVITY HC ₅₀ ($\mu\text{g/mL}$)
R	X	n	<i>E. c.</i>	<i>K. p.</i>	<i>B. s.</i>	
CH ₂ CH(CH ₃) ₂	(CH ₂) ₂ NHC(=NH)NH ₂	4	20	50	6	200
		5	20	25	6	200
	(CH ₂) ₅ NH ₂	4	12	50	6	200
		5	12	50	6	200
	(CH ₂) ₅ NHC(=NH)NH ₂	4	12	50	12	35
		5	12	50	12	8
	(CH ₂) ₂ NH ₂	2	>60	500	8	>200
		3	>500	>500	37	>200
		4	~30	63	8	>200
CH(CH ₃) ₂	(CH ₂) ₂ NH ₂	4	100	500	100	
		5	100	500	100	
CH(CH ₃)CH ₂ CH ₃	(CH ₂) ₂ NH ₂	4	500	500	20	
		5	100	500	20	
C ₆ H ₅	(CH ₂) ₂ NH ₂	4	500	500	100	
		5	500	>500	100	
<i>n</i> -C ₄ H ₉	(CH ₂) ₂ NH ₂	4	500	500	500	
		5	100	500	100	
(CH ₂) ₃ NHC(=NH)NH ₂	Me	4	>500	500	500	
		5	500	500	500	
(CH ₂) ₃ NHC(=NH)NH ₂	<i>ISO</i> -PENTYL	4	100	100	6	4
		5	100	100	12	4
(CH ₂) ₄ NH ₂		2	>500	>500	25	
		4	63	63	<5	

¹ *E.c. Escherichia coli* D31; *K.p. Klebsiella pneumoniae* 10; *B.s. Bacillus subtilis*

FIG.9

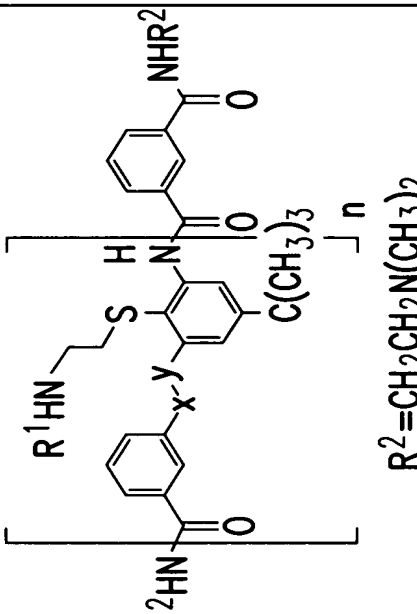
 $R^2=CH_2CH_2N(CH_3)_2$				ANTIMICROBIAL ACTIVITY MIC ($\mu g/ml$)					
-x-y-	R ¹	n	M _p ⁷	K91 ¹	K91 ²	D31 ³	K.p. ⁴	B.s. ⁵	rbc ⁶
-CONH-	H	2	756 ⁸		<18	19	66	12	50
	H	3	1125 ⁸		<19		19		20
	H	10	6000 ⁹	<25	12-50	7.5-15	31-50		1
	H	>30	20,000	>200					5
	C(=NH)NH ₂		6000			25	100	12.5	8
-NHCONH-	H	2	745 ⁸	<12.5					15
	H	10	6000		<50				5
	H	>30	20000		100				20

FIG.10

- ¹ *E. coli* K91 (M9 MEDIUM)
- ² *E. coli* K91 (LB MEDIUM)
- ³ *E. coli* D31 (MH MEDIUM)
- ⁴ *Klebsiella pneumoniae* 10 (MH MEDIUM)
- ⁵ *Bacteria subtilis* (LB MEDIUM)
- ⁶ HEMOLYTIC ACTIVITY-ERYTHROCYTES HC₅₀ ($\mu\text{g}/\text{mL}$)
- ⁷ THE AVERAGE CHAIN LENGTH IS DETERMINED BY THE FLORY EQUATION AND THE POLYMER SIZE IS CONFIRMED BY GEL CHROMATOGRAPHY WITH WATERS STYRYL-GEL COLUMNS WERE CONNECTED IN SERIES TO GIVE A MW RANGE FROM 1,000,000 TO 300. THE PEAK WAS ELUTED WITH THF AND THE PEAK CENTER AT MAXIMUM HEIGHT USING A SIZE EXCLUSION COLUMN. AVERAGE POLYDISPERSITY FOR THESE CONDENSATION POLYMERS IS ~ 2.5 .
- ⁸ HOMOGENOUS COMPOUND PREPARED BY SOLID PHASE SYNTHESIS.
- ⁹ *Pseudomonas aeruginosa* 10 IC₅₀ 31-62; *Salmonella typhimurium*, S5 IC₅₀ <3.75; *Enterococcus faecium* IC₅₀ 15-25 ($\mu\text{g}/\text{mL}$).

FIG.10A

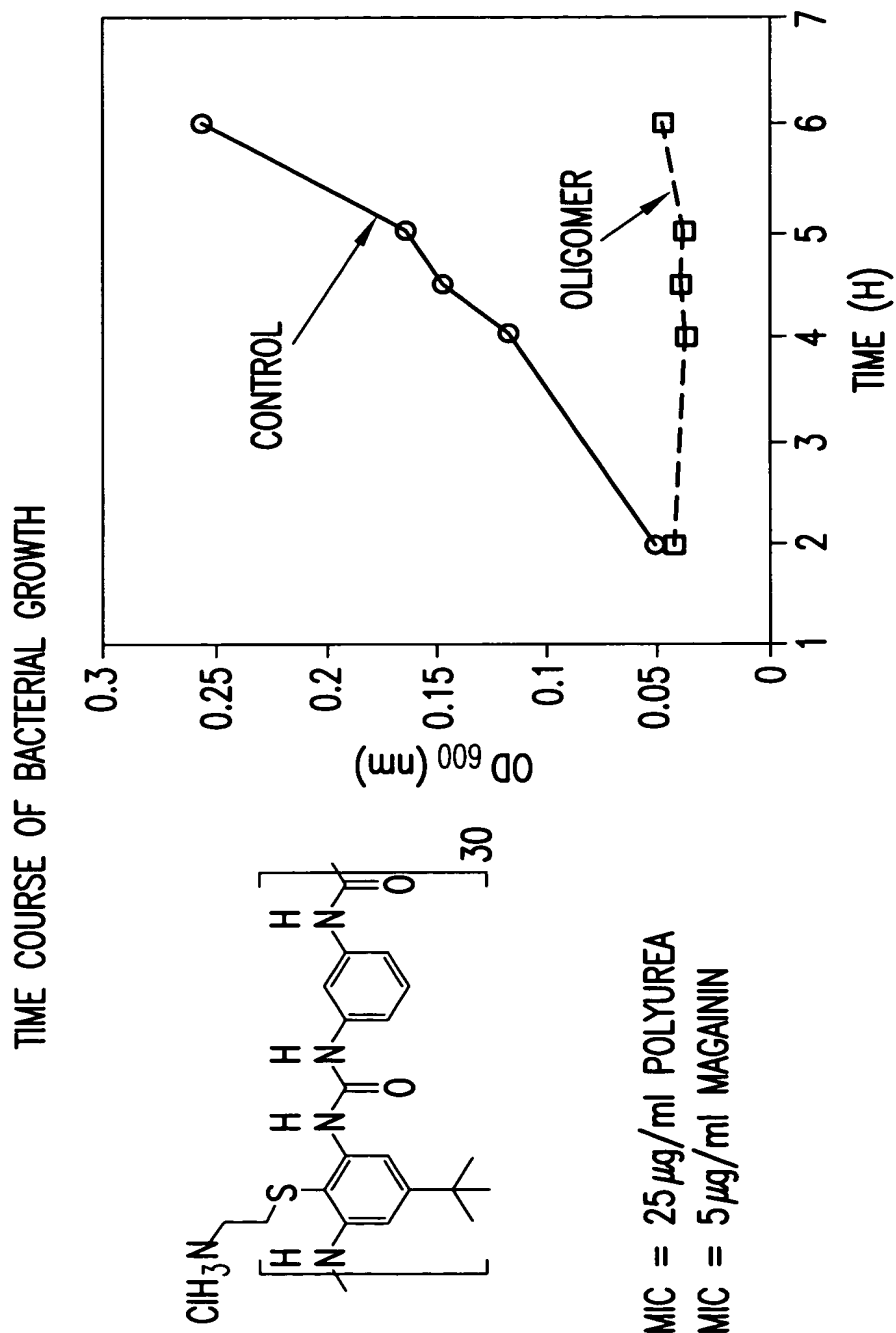


FIG. 11

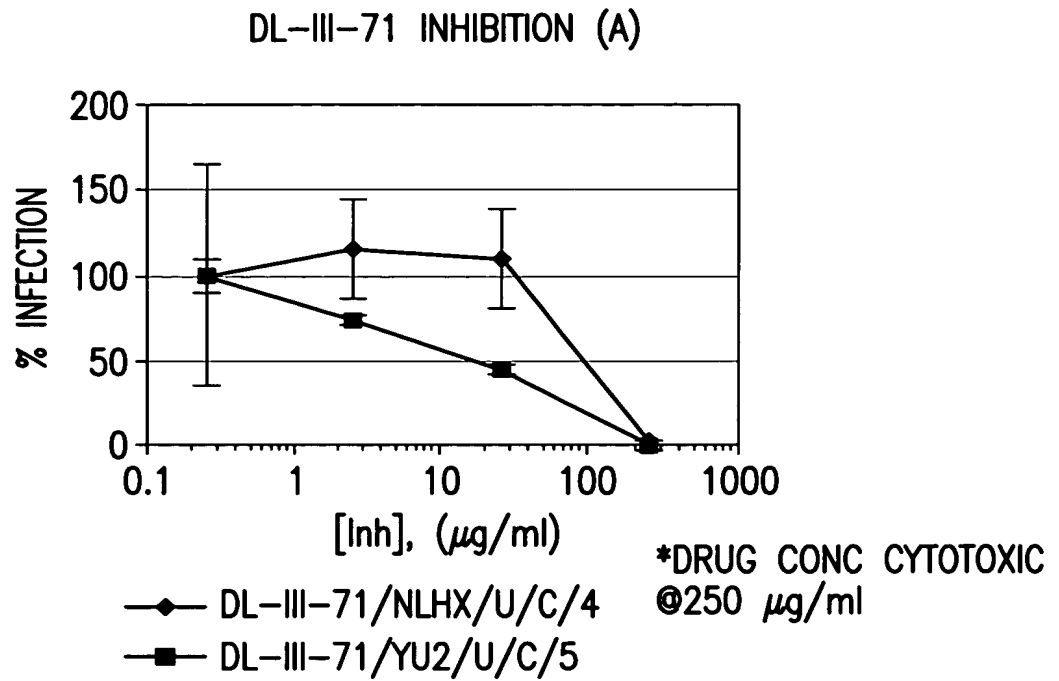


FIG. 12

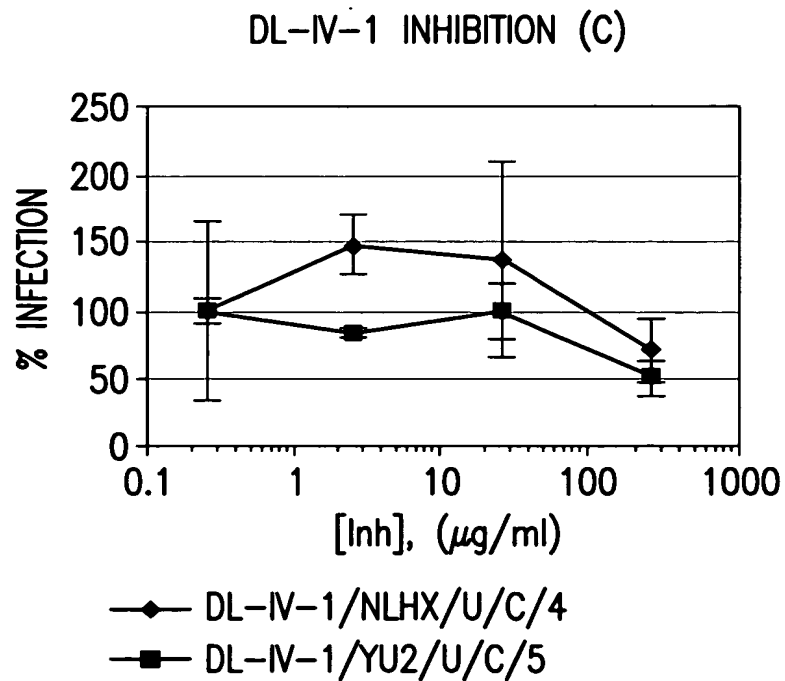


FIG. 13

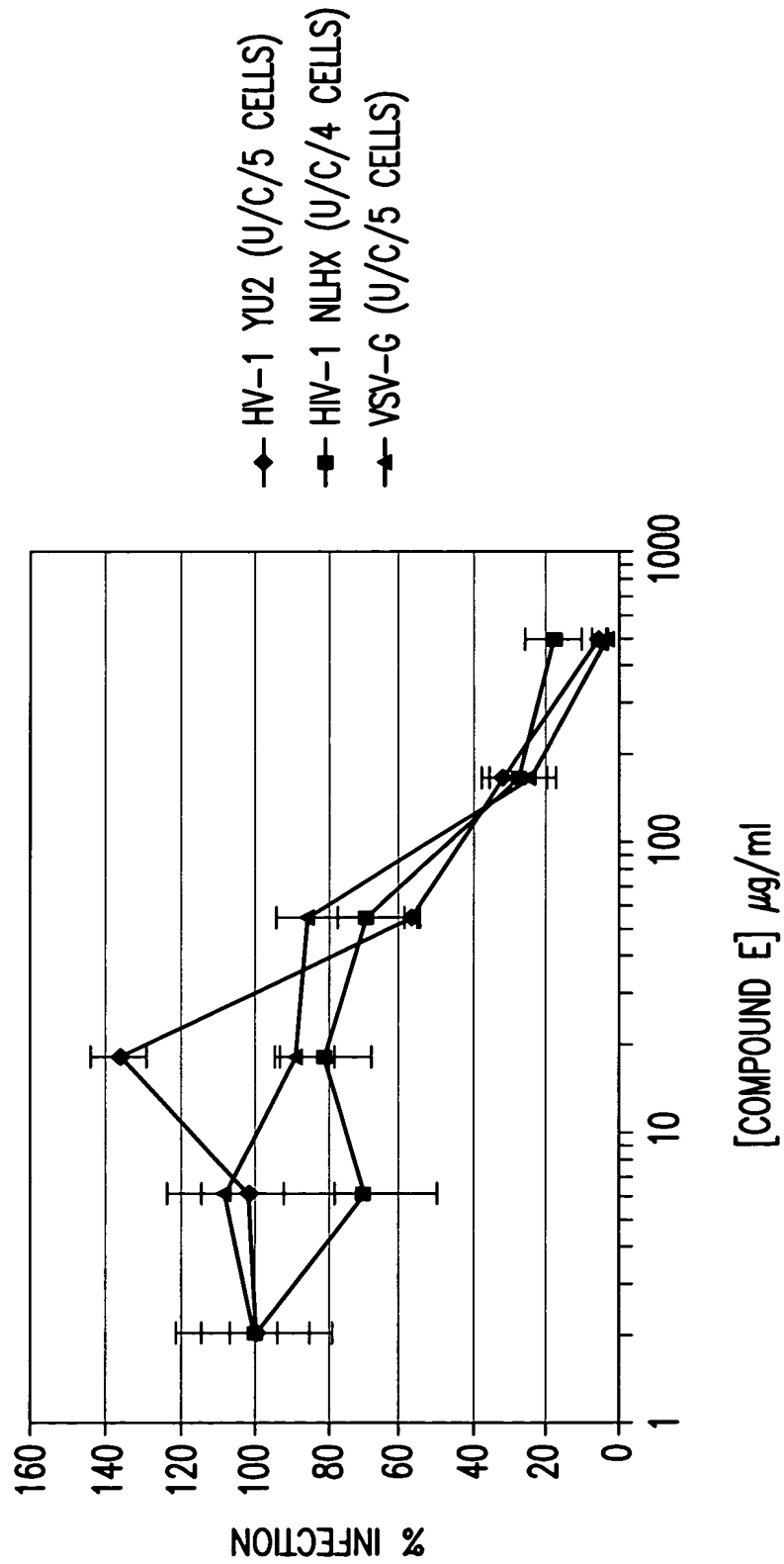


FIG.14

COMPOUND STRUCTURES

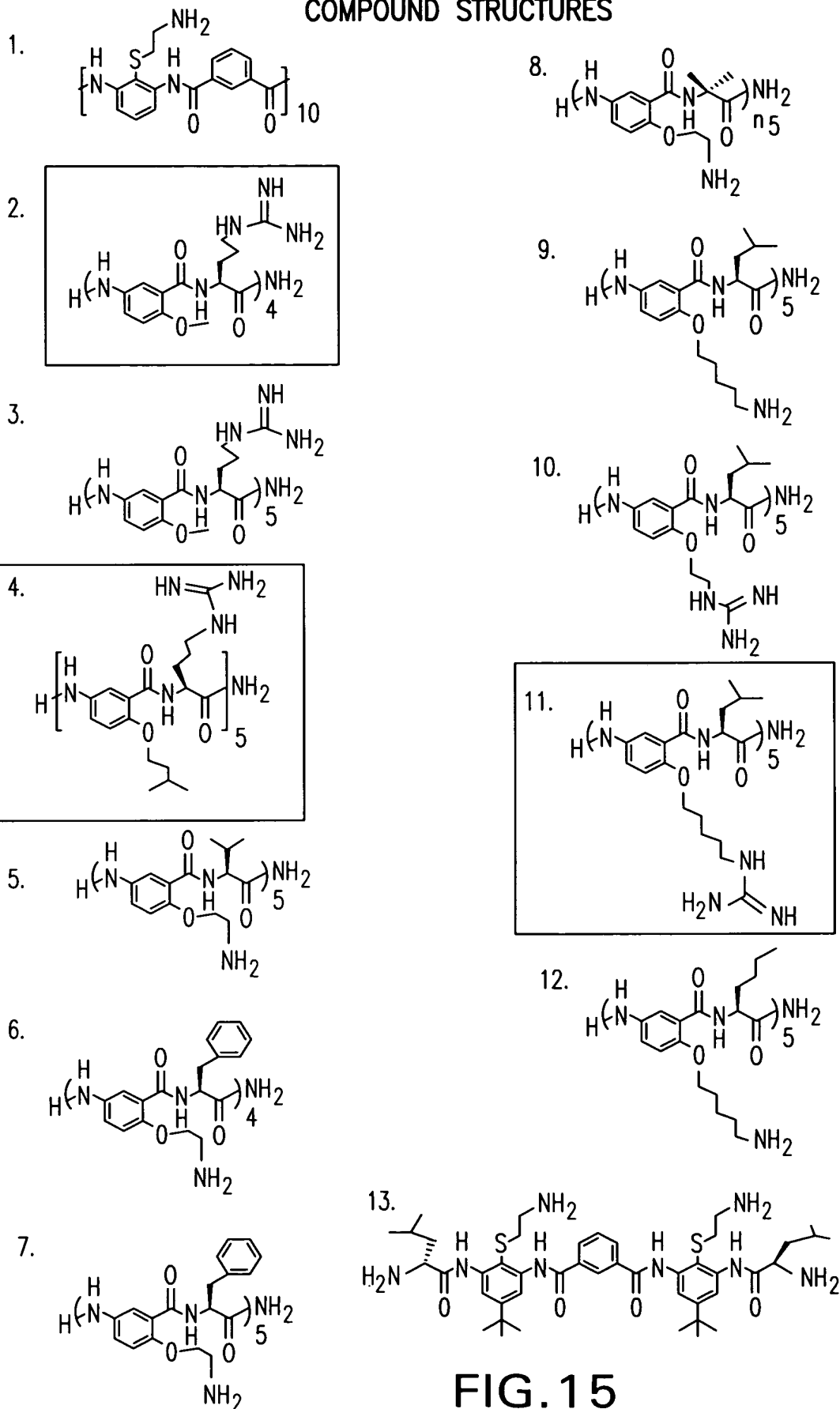


FIG. 15

COMPOUND STRUCTURES

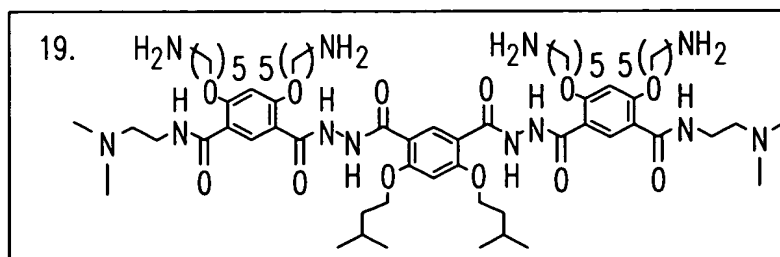
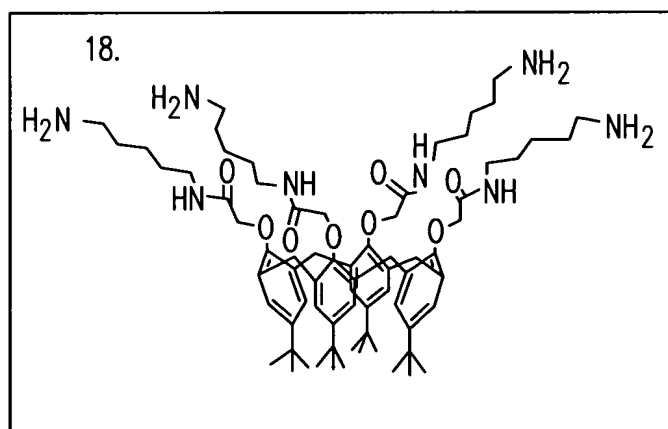
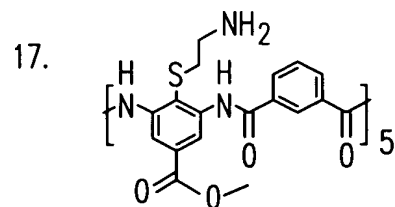
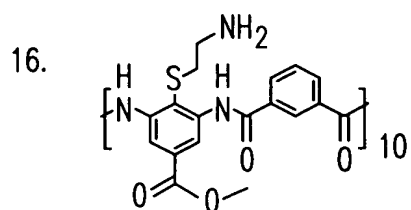
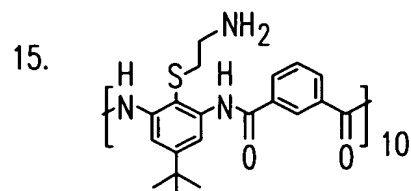
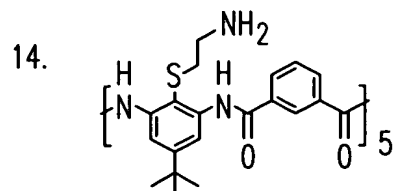
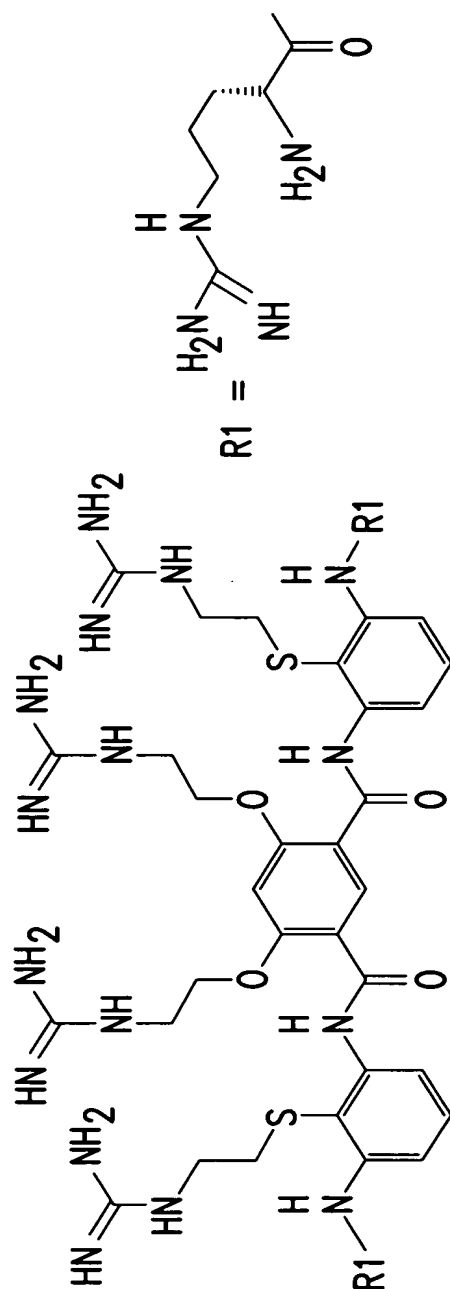


FIG.15A



Pmx10073

FIG.16

ANTAGONISM OF THE LMWH EFFECTS ON CLOTTING TIME IN WHOLE BLOOD BY Pmx10073.

Pmx10073 vs LeoPharm1502990.9-5

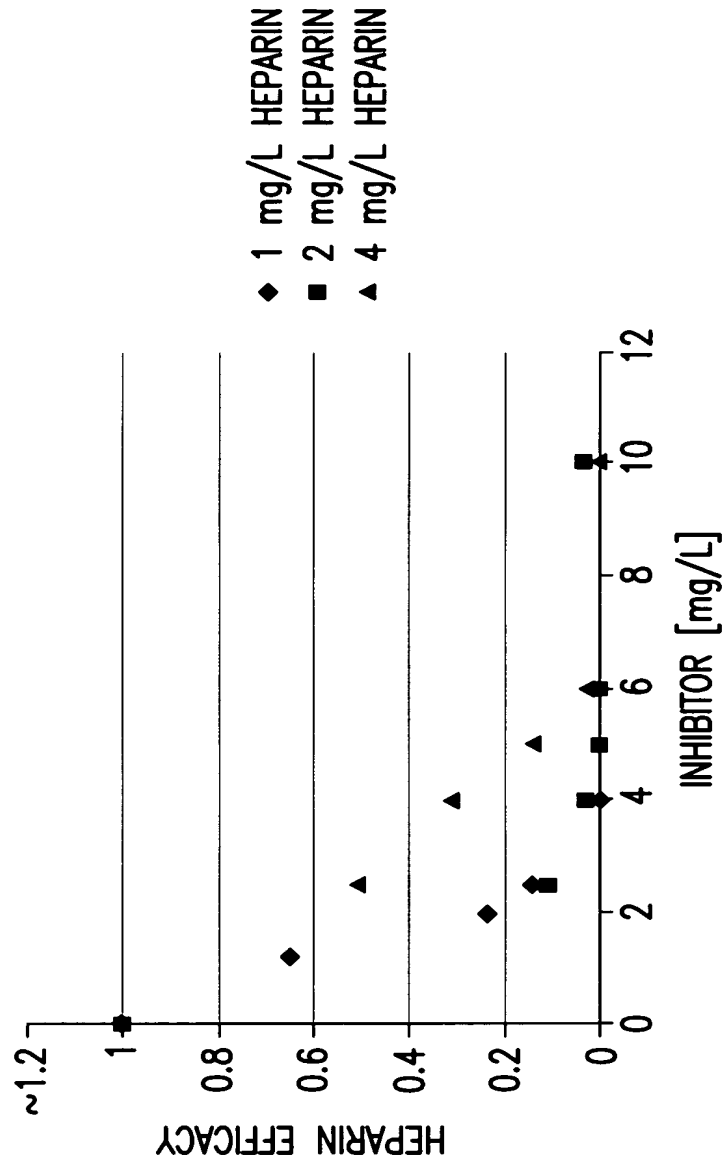


FIG.17

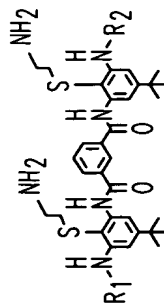


TABLE 1. ANTIBACTERIAL ACTIVITY AND SELECTIVITY.

COMPOUND	R ₁	MIC(μ g/mL)		HC50 (μ g/mL)		SELECTIVITY (HC50/MIC)		RELATIVE HYDROPHOBICITY LogK _{OW}
		E.coli	S.aureus	E.coli	S.aureus	E.coli	S.aureus	
1	H	12.5	50	12	0.24	0.96	3.51	
2		6.25	12	40	3.3	6.4	3.12	
3		6.25	6.25	9	1.4	1.4	3.74	
4		6.25	6.25	7	1.1	1.1	3.86	
5		25	50	790	16	32	1.45	
6		25	100	1230 ^(*)	12	49	2.99	
7		50		370		7.4	0.33	
8		6.25	12.5	715	57	110	-1.71	
MSI-78		12.5		120		9.6		

(*)HC50 WAS OBTAINED FROM EXTRAPOLATING THE FITTED CURVE TO 50% LYSIS

FIG.18

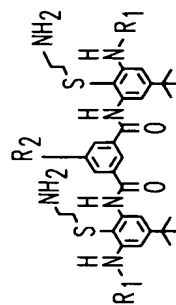
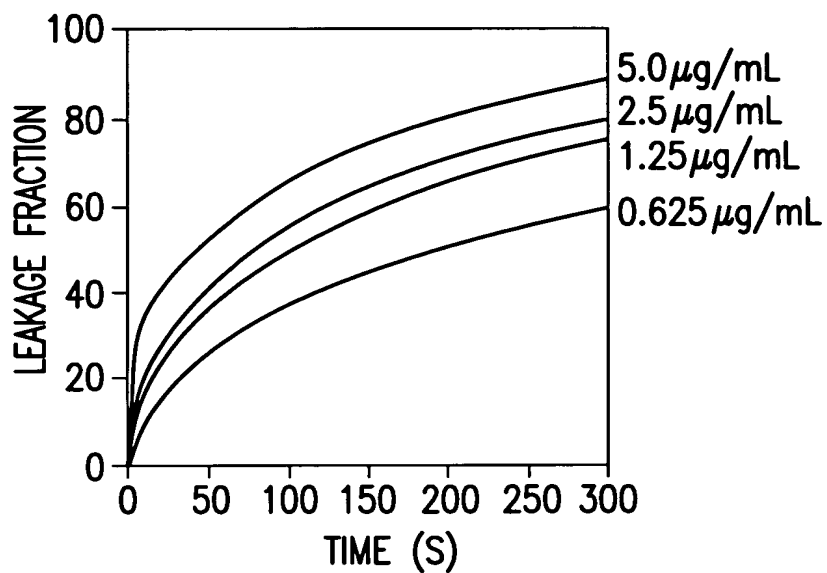


TABLE 2. ANTIBACTERIAL ACTIVITY AND SELECTIVITY (CONTINUED).

COMPOUND	R ₁	R ₂	MIC (μg/mL)		HC50 (μg/mL)		SELECTIVITY (HC50/MIC)		LogK _{OW}	RELATIVE HYDROPHOBICITY
			E.coli	S.aureus	E.coli	S.aureus	E.coli	S.aureus		
1	H	H	12.5	50	12	0.24	0.96	0.24	3.51	
9	H	H ₂ N~O-	25	25	110 ^(*)	4.4	4.4	4.4	2.61	
10		H ₂ N~O-	50	200	400	2.0	8.0	2.0	1.53	
3		H	6.25	6.25	9	1.4	1.4	1.4	3.74	
11		H ₂ N~O-	12.5	12.5	61	4.9	4.9	4.9	2.84	
8		H	6.25	12.5	715	57	110	57	-1.71	
12		H ₂ N~O-	12.5	12.5	>800	>64	>64	>64	-2.61	
MSI-78			12.5		120	9.6				

(*)HC50 WAS OBTAINED FROM EXTRAPOLATING THE FITTED CURVE TO 50% LYSIS

FIG.19



AMPHIPHILIC OLIGOMER 8 INDUCES VESICLE LEAKAGE.

FIG.20